

CHARGE NUMBER: 2500  
PROGRAM TITLE: Synthesis of Tobacco Additives  
PERIOD COVERED: April 1 - 30, 1980  
PROJECT LEADER: J. I. Seeman  
DATE OF REPORT: May 8, 1980

## I. FLAVOR CHEMISTRY

A major effort is underway to prepare 10 pounds of a key oriental flavorant. This substance has shown interesting subjective results at relatively low threshold levels. A number of different chemical steps are required to prepare the material from commercially available and inexpensive reagents. Because of the very large scales involved, the procedures are rather laborious and significant care is being taken to insure positive results.<sup>1-3</sup>

The novel process used to prepare 2-isopropyl-5-keto-hexanoic acid from piperitone was used to prepare a number of additional keto acids from readily available cyclic  $\alpha,\beta$ -unsaturated ketones. A literature search was carried out and there is no prior art regarding this oxidation procedure.<sup>2</sup>

Ethyl vinyl ketone and isopropyl vinyl ketone were each reacted with the pyrrolidine enamine of isovaleraldehyde to give the corresponding 2-isopropyl-5-ketoheptanal and 2-isopropyl-5-keto-7-methyloctanal. These materials will be oxidized to the related keto acids which are analogues of 2-isopropyl-5-ketohexanoic acid. The alkyl vinyl ketones were prepared by reaction of the alkylcarboxylic acids with vinylolithium.<sup>4</sup>

Approximately 2.5g of 12Z-abienol was obtained from careful HPLC purification of a small portion (5g) of oil isolated from 200g of Canadian balsam. Some 50g of the oil remains for additional preparation the 12Z-abienol which was identified by  $^{13}\text{C}$  nmr spectroscopy. Abienol is expected to be

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a key precursor of a number of potentially interesting tobacco flavorants. Effort is also being made to use this labdane terpenoid as the starting point for the preparation of terpenoid flavorants found in a variety of tobaccos.<sup>5</sup>

Reaction of methylpyrazine with LDA/isopropylbromide gave isobutylpyrazine (15%) along with two new pyrazines, 2,3-diisobutylpyrazine and 2,4-dimethyl-3-pyrazylpentane, a highly branched, monosubstituted pyrazine. The latter has a tea-like aroma similar to Bright tobacco. All three will be evaluated shortly.<sup>5</sup>

Methylmagnesium chloride was reacted with  $\alpha$ -butyliodo-cyanate to give a mixture of WS-14 and neo-WS-14. A large sample of ethyl 2-sec-butyl-3-hydroxy-3-phenylbutanoate, an ethyl  $\beta$ -methylvalerate:acetophenone release agent, was prepared.<sup>1</sup>

## II FLAVOR RELEASE

The two major products resultant from the self-condensation of 3-acetylpyridine have now been identified as the dimeric 3-pyridyl 2-(3-pyridyl)-1-propenyl ketone and the trimeric derivative, the latter presumably formed by the addition of the anion of 3-acetylpyridine to the dimer. Pyrolysis of the sodium salt of 2-sec-butyl-3-hydroxy-3-(4-pyridyl)butanoic acid gave 4-acetylpyridine and sodium  $\beta$ -methyl valerate. No olefin, which would have resulted from dehydration, was observed. Nonetheless, the pyrolysis was not as clean as that found for the 3-pyridyl analogue.

Sodium 2-(sec-butyl)-3-hydroxy-(3-pyridyl)butanoate was impregnated on cellulose filter paper and subjected to the standard pyrolysis conditions; significant quantities of  $\beta$ -methylvaleric acid and 3-acetylpyridine (1:1) was obtained along with a trace amount of the dehydration product. This demonstrates that the salt releases the free acid in the presence of water.<sup>6</sup>

In a most unusual result, the reaction of phenylacetone with diethylcarbonate and sodium hydride led to a mixture of phenylacetic acid and diethyl phenylmalonate. An interesting series of reactions has been proposed to account for the results. Further attempts to prepare a ketone release agent are in progress.<sup>7</sup>

The reaction of a number of carboxylic acids with simple sugars in the presence of carbonyldimidazole affords sugar esters of unknown structure. Careful nmr analysis has not yet allowed the determination of the position(s) of esterification. These materials are expected to provide interesting acid release systems.<sup>7</sup>

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Approximately 400g of poly(monomenthyl itaconate) has been prepared. Hydrogenation of the product is being completed to remove any residual monomer unsaturation.<sup>8</sup>

1-O-(3-methylvaleryl)- $\alpha$ -D-mannopyranose was prepared in a number of steps from  $\beta$ -methylvaleryl chloride and the protected mannopyranose derivative. This will be tested as a  $\beta$ -methylvaleric acid release agent. It has the particular advantage of being water soluble and mostly "sugar-like."<sup>8</sup>

Preparation of vinyl ethyl *sec*-butylmalonate was carried out. This material was polymerized and will serve as an ester release agent, in this case releasing ethyl  $\beta$ -methylvalerate.<sup>5,8</sup>

### III ALKALOID CHEMISTRY

The reaction of 3-pyridyllithium with N-methylpyrrolidinone followed by acid treatment and extensive purification led to a beautifully crystalline sample of N'-methylmyosmine diperchlorate. Conditions were found to obtain 2'-methylnicotine from the above diperchlorate by reacting it with 0.95 equiv of methylolithium at low temperature.<sup>9</sup>

Two very interesting 6-substituted nicotine analogues have now been prepared: 6-isopropynicotine and 6-cyclopropynicotine. These are particularly valuable due to the structural similarity of an isopropyl group and a cyclopropyl group. As part of a study aimed at determining the racemization step in the asymmetric nicotine synthesis, (S)-(-)-1-methyl-2-cyanomethylpyrrolidine was treated with LDA under the previously used alkylation conditions; recovered starting material (75%) had an identical rotation to that observed before the reaction. Efforts continue toward the preparation of additional bridged nicotines. Alkylation of 7,8-dihydro-5(6-H) quinolone with LDA/t-butylbromoacetate led to alkylated product in 50% yield. Attempts to reductively aminate this keto ester failed.<sup>10</sup>

### IV. REFERENCES

1. DeBardeleben, F. 7310
2. Edwards, W. B. III, 7415
3. Because of the nature of this project, a major group effort is being undertaken to lend assistance whenever required.
4. Williams, D. 7448
5. Southwick, R. 7446
6. Houminer, Y. 7424
7. Chan, G. 7341
8. Grubbs, H. 7361
9. Secor, H.V. 7386

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